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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,317	10/15/2003	Susan M. Freier	IBIS0009-101 (ISPH-0794)	8250
34138	7590	11/14/2006	EXAMINER	
ISIS PHARMACEUTICALS, INC 1896 RUTHERFORD ROAD CARLBAD, CA 92008			VIVLEMORE, TRACY ANN	
			ART UNIT	PAPER NUMBER

1635

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 10/686,317	Applicant(s) FREIER ET AL.	
	Examiner Tracy Vivlemore	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 21 June 2006.  
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.  
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 17 and 32-42 is/are pending in the application.  
4a) Of the above claim(s) 32-38 is/are withdrawn from consideration.  
5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.  
6) ☒ Claim(s) 17 and 39-42 is/are rejected.  
7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.  
8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.  
10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

### ***Election/Restrictions***

Applicant's election of the activity-enhancing motif of CCAC and the activity-decreasing motif of GGGG in the reply filed on June 21, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

### ***Response to arguments: Claim Rejections - 35 USC § 102***

Claims 17, 39 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Stewart et al. (Biochemical Pharmacology, 1996, of record). This rejection is maintained for the reasons set forth in the office action mailed August 16, 2005 and clarified below.

Applicant argues that the rejection over Stewart et al. is moot in view of the amendments to claim 17. This argument is not persuasive because Stewart et al. disclose in table 1 a set of antisense oligonucleotides targeted to MRP. One of these sequences, designated as ISIS 7594, meets the limitations of the claims as amended by containing a CCAC motif and lacking a GGGG motif. Stewart further synthesizes this

oligonucleotide and tested *in vitro* its ability to modulate a target nucleic acid, meeting the limitations of claims 39 and 42.

***Claim Rejections - 35 USC § 103***

Claims 17 and 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stewart et al. as applied to claims 17, 39 and 42 in the 102 rejection above, and further in view of Baracchini et al. (US 5,801,154).

Claims 17, 39 and 42 are directed to methods of selecting effective antisense oligonucleotides, synthesizing such oligonucleotides and testing their activity *in vitro*. Claims 40 and 41 depend from claim 39 and recite that the antisense oligonucleotides synthesized are chimeric and may contain at least one 2'-substituted nucleotide.

Stewart et al. teach a set of antisense oligonucleotides targeted to MRP. One of these oligonucleotides, ISIS 7594, meets the limitations of claim 17 by having a CCAC motif and lacking a GGGG motif. This oligonucleotide was synthesized by Stewart et al. and its efficacy was tested *in vitro*. Stewart et al. do not teach chimeric oligonucleotides comprising a 2'-substituted nucleotide.

Baracchini et al. teach that preferred antisense oligonucleotides are modified in their sugar, backbone linkage and nucleobase composition (col. 6). Baracchini teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Baracchini et al. teach at column 8 chimeric oligonucleotides comprising 2'-substituted nucleotides.

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It would have been obvious to one of ordinary skill in the art at the time the invention was made to synthesize the oligonucleotides taught by Stewart as chimeric oligonucleotides comprising a 2'-substituted nucleotide. Baracchini et al. provide a motivation to do so, teaching that antisense oligonucleotides that comprise modified nucleotides have increase cellular uptake and nuclease resistance and that one preferred type of modification is the use of a chimera comprising 2'-substituted nucleotides. One of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of Stewart et al. and Baracchini et al. because Baracchini et al. teach that the synthesis of oligonucleotides comprising modified nucleotides is routine in the art.

Thus, the invention of claims 17 and 39-42 would have been obvious, as a whole, at the time of invention.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file

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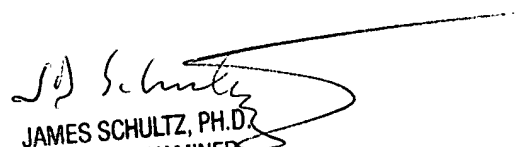
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folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore  
Examiner  
Art Unit 1635

TV  
October 31, 2006

  
JAMES SCHULTZ, PH.D.  
PRIMARY EXAMINER